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TITLE: Evaluation of Feasibility for a Case-Control Study of
Adrenal Androgen Production in Postmenopausal Women with
Breast Cancer

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13. ABSTRACT (Maximum 200 Words) Background: Postmenopausal women with elevated serum estrogens and androgens are at an increased risk of breast cancer. Dehydroepiandrosterone sulfate (DHEAS) is secreted only by the adrenals, and elevated serum DHEAS levels in postmenopausal women who develop breast cancer suggest increased adrenal androgen production. Objective/Hypothesis: We will evaluate the feasibility of conducting a case-control study that uses adrenocorticotrophic hormone (ACTH) stimulation tests to determine if postmenopausal women who develop breast cancer secrete more adrenal androgens, which are converted to estrogens in peripheral tissues, in response to ACTH stimulation compared to unaffected women. Hypotheses to be tested in the full-scale study are: 1) greater adrenal responsiveness to ACTH contributes to elevated serum concentrations of androgens and estrogens in postmenopausal women who develop breast cancer; and 2) increased adrenal androgen production in postmenopausal women with breast cancer is related to increased enzyme activity at a specific step in steroidogenesis. Specific Aims: Specific aims of the feasibility study are: 1) determine the feasibility of a full-scale study; 2) gather preliminary data on basal and ACTH stimulated serum concentrations of dehydroepiandrosterone (DHEA), androstenedione, testosterone, estradiol, and estrone in women with breast cancer compared to controls. Study Design: A case-control study will be conducted at FCCC.				
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Introduction: Postmenopausal women with elevated serum estrogens and androgens are at an increased risk of breast cancer. Dehydroepiandrosterone sulfate (DHEAS) is secreted only by the adrenals, and elevated serum DHEAS levels in postmenopausal women who develop breast cancer suggest increased adrenal androgen production. The objective of the pilot study is to evaluate the feasibility of conducting a case-control study that uses adrenocorticotrophic hormone (ACTH) stimulation tests to determine if postmenopausal women who develop breast cancer secrete more adrenal androgens, which are converted to estrogens in peripheral tissues, in response to ACTH stimulation compared to unaffected women. Hypotheses to be tested in the full-scale study are: 1) greater adrenal responsiveness to ACTH contributes to elevated serum concentrations of androgens and estrogens in postmenopausal women who develop breast cancer; and 2) increased adrenal androgen production in postmenopausal women with breast cancer is related to increased enzyme activity at a specific step in steroidogenesis rather than to generalized enhancement of adrenal androgen production. Cellular immune function also has been hypothesized to play a role in breast cancer etiology, and cortisol, which is another hormone that is secreted by the adrenals, is immunosuppressive (i.e., causes significant decreases in numbers and percentages of lymphocytes in the blood). At no additional cost to DOD we are also collecting preliminary data to begin to address the hypothesis that greater adrenal responsiveness to ACTH contributes to greater immunosuppression in postmenopausal women who develop breast cancer.

Body: Research accomplishments are described for each task outlined in the approved statement of work.

Task 1. Prepare for data collection, Month 1-2

- a. Finalize data collection protocol and forms. This activity has been completed and all questionnaires have been approved by both the FCCC IRB and the DOD IRB.
- b. Finalize database design and data entry screen. This activity has been completed.
- c. Hire and train study coordinator. This activity has been completed, but changes in personnel have delayed progress. These personnel changes have been motivated by career decisions, Leigh Coakley completed nursing school and left to take a nursing position at a local hospital, and Chris Chatham, who replaced Leigh, left soon after to take another better paying position. Deb Riordan assumed the study coordinator position April 21, 2003, completed all human subjects and HIPPA training for certification and has been trained in all aspects of the study. We also have added a senior clinical research coordinator, Cecilia McAleer BS, CCRP, who works in the FCCC protocol office and has extensive experience in conducting clinical studies at FCCC. She is responsible for coordinating participant scheduling, preparing treatment orders, and ensuring that the appropriate staff are notified to collect and process the blood specimens. She will also assist with administering questionnaires and ensuring that all necessary forms are completed. She also has been trained in all aspects of the study.

Task 2. Identify and recruit participants, Months 2-6

- a. Search FCCC Breast Evaluation Clinic and breast surgical consultation visit summaries each day to identify potential cases and benign breast disease controls. The FCCC IRB required that we conduct the study in phases – recruiting and conducting dexamethasone suppression and ACTH stimulation studies on healthy controls during the first phase, on spouses of cancer patients during the second phase, and on women who had breast cancer during the third phase. A FCCC Data Safety and Monitoring Board and the DOD IRB will review results after each phase before we can proceed to the next phase. Because we are currently recruiting healthy controls for phase 1, via advertisements and posters that have been approved by the FCC and DOD IRB's, this activity has not been initiated. Note that benign breast disease controls have been replaced by spouses of cancer patients to control for chronic psychological stress associated with being diagnosed with cancer or with a spouse being diagnosed with cancer. There also was concern that benign breast disease controls may not be appropriate because elevated hormone levels have been associated with benign breast disease in some studies.
- b. Obtain physician approval to contact cases and benign breast disease controls. For the reasons described above under (a), this activity has not been initiated.
- c. Identify one friend control who is eligible and agrees to participate for each case: Friend controls have been replaced with healthy community controls because of the IRBs concerns about asking cases to identify friends who did not have breast cancer.
- d. Perform approximately 60 telephone interviews. As of May 28, 2003, 42 postmenopausal women responded to the advertisement and called Fox Chase for more information. Of these women, 13 were not eligible for participation based on the preliminary screening questionnaire approved by the FCCC and DOD IRBs. Thirteen women were not interested once they received more information about the study. We identified 9 women who are potentially eligible. An additional 7 women have been sent study materials and will be recontacted to determine their interest in the study and potential eligibility.
- e. Send approximately 30 follow-up letters. Letters have been sent to 16 people.

Task 3. Conduct data collection visits, Months 2-8. We are waiting for DOD IRB approval of changes to the protocol submitted in June 2003 before beginning data collection visits. These changes have been approved by the FCCC IRB.

- a. Administer 30 questionnaires.
- b. Measure heights and weights of 30 participants.
- c. Perform 30 ACTH stimulation tests, collect and store serum specimens
- d. Extract DNA from lymphocytes for 30 participants and store
- e. Key and verify data

Task 4. Create serum and plasma pools for laboratory quality control, Month 8. This task will be done when we get closer to conducting laboratory analyses.

Task 5. Measure the ACTH concentration in plasma and DHEAS, DHEA, androstenedione, testosterone, estradiol, concentrations in serum from 30 participants, Months 9-10. This task will be done after conduct of dexamethasone suppression and ACTH stimulation

studies. Note that the FCCC IRB required that we perform interim analyses of DHEA after each phase of the study before progressing to the next phase and obtain approval of the Data and Safety Monitoring Board before progressing to the next phase. The DOD IRB has required that they also review the results and approve before we proceed.

Task 6. Analyze data and write reports, Months 11-12. This task will be completed in the future.

- a. Perform statistical analyses
- b. Write final report
- c. Begin writing grant proposal for full scale study

Key Research Accomplishments:

- a. Our goal for the first phase of the study is to recruit 7 women.
- b. We have identified 9 women who are interested in participating and are potentially eligible.
- c. An additional 7 women have been sent study materials and will be recontacted to determine their interest in the study and potential eligibility.

Reportable Outcomes: None at this time.

Conclusions: This is an interim report for a pilot study. Based on our experience to date, it appears that we will be able to recruit healthy controls for a full scale case-control study that uses adrenocorticotrophic hormone (ACTH) stimulation tests to determine if postmenopausal women who develop breast cancer secrete more adrenal androgens, which are converted to estrogens in peripheral tissues, in response to ACTH stimulation compared to unaffected women. The full-scale study will also determine if greater adrenal responsiveness to ACTH contributes to greater immunosuppression in postmenopausal women who develop breast cancer. This is one of the first studies to examine, in an integrated approach, the interrelationships of hormonal and immune responses to adrenal suppression and stimulation in women with breast cancer in comparison to healthy controls. Identification of a role for the adrenals in the etiology of breast cancer in postmenopausal women could ultimately lead to detection of populations at an increased risk of breast cancer, provide an approach to screening for women at increased risk, and/or lead to chemopreventive strategies that target the responsible enzyme or regulatory protein.

References: None at this time.

Appendices: None at this time.